Clostridoides difficile

NDAFP 2024

Big Sky

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Objectives

1. Understand the burden of C. difficile in America
2. Testing: Know whom to test, which test, and avoid unnecessary testing
3. Know how to treat C. difficile and severe associated infection

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Sources

- 2018 IDSA and Society for Healthcare Epidemiology of America (SHEA)
- 2020 AFP review of C. Diff Guidelines
- 2021 IDSA SHEA focused update for C. Difficile infection
- American College of Gastroenterology & American Society for Microbiology

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Terminology

- Clostridioides difficile [klos–TRID–e–OY-dees dif–uh–SEEL] (C. diff

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Terminology Geek

- Clostridium difficile was reclassified in 2016 when it became necessary to **assign C difficile to a new genus**
- Following the restriction of the genus to Clostridium butyricum and related species in 2015
- Initially described 1978, anaerobic, Gram-positive, spore-forming rod
- Creating a genus that began with the letter C, so relevant abbreviations remained unchanged

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Epidemiology

- CDC: C. diff is a major health threat
- 223,900 cases in hospitalized patients and 12,800 deaths in the United States 2017
- C. difficile is more prevalent in diarrheal stools obtained >72 hours after admission
- Colonization is common in hospitalized patients and residents of long-term care facilities
- Asymptomatic carriage is recognized, patients without diarrhea should not be tested or treated.
  - Labs exclude testing on formed stool
- 1 in 6 patients who get C. diff infection will get it again in the subsequent 2-8 weeks

Guh AY, Mu Y, Winston LG et al. N Engl J Med 2020;382:1320–30. DOI: 10.1056/NEJMoa1910215

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Epidemiology Continued

- 2011, an estimated one million infections and 29,000 deaths were attributed to *C difficile*
- One in 11 people over 65 diagnosed with a healthcare-associated C. diff infection die within a month
- People are 7-10x more likely to get C. diff infection while taking an antibiotic or the ensuing month
- More than 80% of C. diff deaths occur in people 65 or older

Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825–34. DOI: 10.1056/NEJMoa1408913

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Epidemiology in Children

- The high frequency (up to 70%) of asymptomatic colonization among healthy newborns
- Rates gradually fall to adult levels as the microbiota of the lower intestine becomes established by about 2 years of age
- For children ages 1 to 3 with diarrhea, testing can be considered but other causes (eg, viral) should be considered first.
- Routine testing in children <1 should be avoided given the high carriage rates of C difficile
- For children >3, testing considerations are the same as for adults.
- Although C difficile can colonize neonates/infants, they may lack the cellular machinery to bind and process Clostridium toxins.

IDSA 2017 diarrhea guideline

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Recurrent CDI Epidemiology

- 31,300 community-associated 2017
- 38,500 recurrences for healthcare-associated 2017
- 1 in 6 people who get C. diff infection will get it again in the subsequent 2-8 weeks
- Compromised immunity
- Severe CDI
- Ribotype 027/078/244 infections
- 1 or more episodes in last 6 m

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The Microbiome

- Colonization with C. difficile is common in elderly patients
- Community-acquired C. difficile; some strains appear to be genetically distinct from hospital strains

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What is the significance of c diff in the healthcare setting

- *O*pportunistic
- Toxin-producing bacterial GI infection
- Elderly
- Long Term Care
- 25% to 30% of antibiotic-associated diarrhea
- >95% of pseudomembranous colitis cases
- Incidence doubled since 1996

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What is the significance of c diff in the healthcare setting 2

- Mortality rate is rising owing to emergence of a hypervirulent strain (027/NAP1/B1)
- Disease-causing *C difficile* strains produce 1 or both of 2 toxins:
- toxin A is an enterotoxin and toxin B is a cytotoxin.
- Other strains produce neither toxin and are thought to colonize the colon without causing disease.

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Risk Factors: Antibiotics

- Up to 85% of patients with C. difficile provide a history of exposure to antimicrobial agents within the previous 28 days
- Cephalosporins, β-lactam/β-lactamase inhibitors, clindamycin, and quinolones
- Antibiotic Stewardship reduces rate of C. diff infection

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Impact of Risk Factors

Risk Factor	Odds Ratio
Abnormal Findings on CT	13.5
Minimum Albumin < 2.5	3.44
Age >70	3.35
Small Bowel Obstruction or Ileus	3.06
WBC > 20,000	2.77
Cr > 2	2.4
Recent hospitalization within 30 d	1.39
SNF or Rehab	1.11

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Other Risk Factors

- Antibiotic use
- Gastrointestinal surgery
- Small bowel obstruction
- Obesity
- Hematopoietic stem cell and solid organ transplantation
- Hyperglycemia, hypoalbuminemia, and leukocytosis
- Severe illness
- Gastric acid suppression
- Enteral feeding
- Inflammatory bowel disease
- Cirrhosis
- Peripartum
- Chronic kidney disease

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Which Antibiotics?

Antibiotic	Odds ratio (95% CI)*
Clindamycin	16.80 (7.48 to 37.76)
Cephalosporins, monobactams, and carbapenems	5.68 (2.12 to 15.23)
Fluoroquinolones	5.50 (4.26 to 7.11)
Penicillin	2.71 (1.75 to 4.21)
Macrolides	2.65 (1.92 to 3.64)
Sulfonamides and trimethoprim	1.81 (1.34 to 2.43)
Tetracyclines	0.92 (0.61 to 1.4)

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When to test for C. difficile

- Testing may be considered for C. difficile in people >2 years of age who have a history of diarrhea following antimicrobial use and in people with healthcare-associated diarrhea
- A single diarrheal stool specimen is recommended for detection of toxin or a toxigenic C. difficile strain (eg, NAAT)
- Multiple specimens do not increase yield.

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Who to test

- People 65 and older who take antibiotics and receive medical care
- People staying in hospitals and nursing homes for a long period of time
- People with weakened immune systems or previous infection with C. diff
- 7-10x more likely to get C. diff after taking antibiotics

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Symptoms of C. difficile

- Watery diarrhea three or more times a day for more than one day
- Symptoms often begin within 5 to 10 days after starting an antibiotic. But symptoms can occur as soon as the first day or up to three months later.
- fever
- Abdominal tenderness
- Loss of appetite
- Nausea
- Mild belly cramping and tenderness.

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Signs of C. difficile

- Watery diarrhea as often as 10 to 15 times a day
- Severe Abdominal Pain
- Tachycardia
- Dehydration
- Fever
- Increased white blood cell count
- Kidney failure
- Loss of appetite
- Swollen belly
- Weight loss
- Blood or pus in the stool

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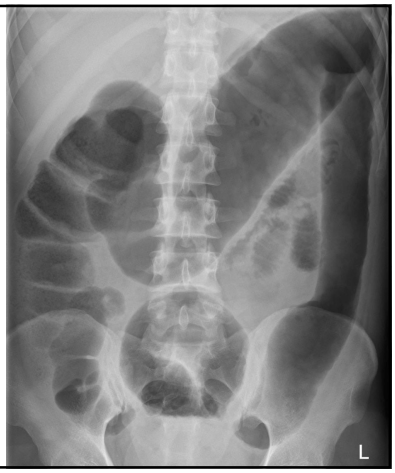
Toxic Megacolon



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Who should be tested?

- Patients with recent or current antibiotic use
- ≥3 episodes of non-formed stool within 24 hours
- Anorexia
- Leukocytosis
- No known ileus obstruction
- Repeat testing to determine cure is not recommended.

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Usually don't test, don't treat Self Resolving

- Most acute diarrhea episodes in previously healthy, immunocompetent people are of short duration and self-resolving, and are of viral or unknown etiology.
- Therefore, laboratory investigation generally is not warranted

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(Tangent) Prevention of Diarrhea

- Reduction of acute infectious diarrhea also can be achieved through general measures, including use of hand hygiene
- Proper food preparation and storage
- Avoidance of high-risk foods such as undercooked meat and seafood
- Unpasteurized milk
- Soft cheese made with unpasteurized milk
- Avoidance of unsafe water

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Which Test, ….. Gold standard

- The *C difficile* cytotoxicity assay has served as a historical gold standard for diagnosing clinically significant disease caused by *C difficile*
- It is not timely for diagnosis
- This assay is best utilized as a reference method or epidemiologic tool

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New Test Strategy

- C diff GDH Stl Ql
- CLOSTRIDIUM DIFFICILE TOXIN/GDH W/REFL TO PCR

SEE NOTE

CLOSTRIDIUM DIFFICILE TOXIN/GDH W/REFL TO PCR

Micro Number:	16327709
Test Status:	Final
Specimen Source:	Stool
Specimen Quality:	Adequate
GDH Antigen:	Not Detected
Toxin A and B:	Not Detected
COMMENT:	No toxigenic C. difficile detected For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ136 (This link is being provided for informational/educational purposes only.)

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Which tests do guidelines recommend for CDI dx

- GI/ Micro: 2 different testing options
  - Nucleic acid amplification tests (NAAT) for *C difficile* toxin genes (test code 16377)
  - 2- or 3-step algorithm that includes assessment of *C difficile* toxin and **glutamate dehydrogenase (GDH)antigen,** (present in all C. diff isolates) as well as detection of the *C difficile* toxin B gene (test code 91664)
- IDSA/SHEA recommend **gene detection** for confirmation when the GDH test is positive and toxin is not detected
- & Recommend gene detection when the GDH test is negative and toxin is detected
- PCR or another nucleic acid amplification test (NAAT) can be used

American College of Gastroenterology & American Society for Microbiology
IDSA/SHEA 2022

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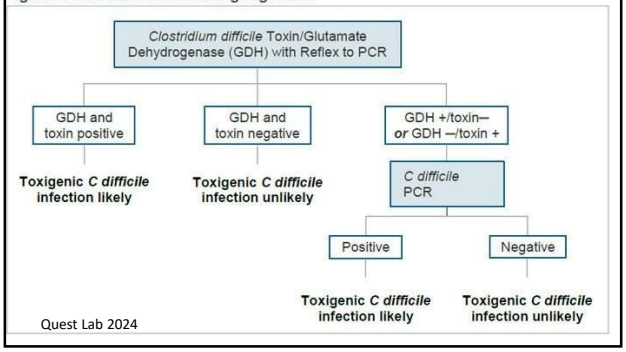
C. Diff testing algorithm

Figure. Test Code 91664 Testing Algorithm



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Toxin and GDH (ie from QUEST)

- If (either A or B or both) and GDH are present, the specimen is **considered positive** for toxigenic *C difficile* infection
- If both toxin and GDH are absent, then the specimen is **considered negative**
- Specimens with **discordant** results (ie, GDH-positive but toxin-negative or GDH-negative but toxin-positive)
- Proceed to the second step
- Reflex PCR *C difficile* gene detection test, 6% of cases
- If the gene is detected, results will include genotype information that indicates if the hypervirulent strain (ribotype O27/NAP1/toxinotype III) is present.

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Virtue of GDH and toxin NAAT

- The newer testing methods are **faster** than culture
- Have **higher sensitivity**
- Have **higher specificity** than GDH testing alone
- The 2-step analysis algorithm increases the sensitivity to 90.5% and the specificity to 93%.
- The sensitivity of the stand-alone NAAT is 93.4 % and the specificity is 90.9%.

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Virulent Ribotypes

- Virulent ribotypes (ribotypes 027/078/244)
- Higher risk of recurrence

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Whom To Avoid Testing: Choosing Wisely: IDSA & EPI

BEST PRACTICES IN INFECTIOUS DISEASES

Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Avoid testing for a *Clostridioides difficile* infection in the absence of diarrhea.	Infectious Diseases Society of America
Do not use antibiotics in patients with recent *C. difficile* infection without convincing evidence of need. Antibiotics pose a high risk of *C. difficile* recurrence.	Society for Healthcare Epidemiology of America

Source: For more information on the Choosing Wisely Campaign, see https://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see https://www.aafp.org/afp/recommendations/search.htm.

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Treatment: Fixadomicin

- First FDA approved medication for CDI (2011) in 31 years
- Ease of administration orally similar to oral vancomycin
- Minimal systemic absorption
- More limited activity against enteric commensals (Narrow spectrum)
- Improved sustained clinical response
- Fewer recurrences
- No differences in mortality compared to vancomycin

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Fixadomicin

- $6,000.00 per month
- $4,500 Good RX cupon

Good Rx 1_17_2024

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IDSA 2023 focused update

- Prefer Fidaxomicin orally over Vancomycin orally
  - Vancomycin is an acceptable alternative
- Recurrent CDI should have Fidaxomicin, (standard or extended pulse) Vancomycin po (tapered or extended pulse) or FMT fecal microbiota transplantation
- Recurrent CDI: Bezlotoxumab in addition to antibiotics
  - Accessibility and Availability vary
  - FDA warning: in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk

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Treatment: Oral Vancomycin

- Non-fulminant
  - 125 mg PO q 6 h x 10 days first episode
- Fulminant (off label)
  - 500 mg PO/NG q6h:
  - IV form may be given PO
  - May give with metronidazole IV
  - Consider 500 mg in 100 mL NS retention enema q6h if complete ileus
- Recurrent
  - Extend duration 14 days , or pulse longer

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Fulminant CDI previously known as severe, complicated

- Not common (higher dose and consider enema)
- Intravenously administered Metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present
- No available data supporting the use of fidaxomicin for treatment of fulminant CDI

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First Recurrence

- Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days
- Alternative: Vancomycin by mouth in a tapered and pulsed regimen
  - 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
- Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode

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Bezlotoxumab

- FDA approved October 2016
- First humanized monoclonal antibody against C. difficile toxin B
- One-time infusion at a recommended dose of 10 mg/kg over 60 minutes
- Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics
  - Caution for use in patients with CHF
- Elimination half-life of 18 days
- Measurable antibody concentration in serum up to 3 months
- Patients with primary CDI and no risk factors likewise did not benefit from bezlotoxumab

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Recommendations: When to use Bezlotoxumab

- In settings where logistics are not an issue, patients with a primary CDI episode and with at least 1 other risk factor for CDI recurrence
- Value Judgments: Equity, Economy
- Cost-Effective Analysis (conducted by Industry)
  - $25,000 per QALY for pt > 65 and at least one recurrence in previous 6m
- Bezlotoxumab plus vancomycin was less cost-effective than vancomycin **for first recurrence** in outpatients

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Real World Use of Bezlotoxumab

- Mostly outpatient Infusions
- PCPs making referrals without ID or GI consultations
- Insurance Denials
- Requires patient selection and advocacy

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Metronidazole for <18

- Fidaxomicin not currently recommended for people <18 years of age
- Metronidazole is still acceptable treatment for nonsevere CDI in children and as a second-line agent for adults with nonsevere CDI (eg, who cannot obtain vancomycin or fidaxomicin at a reasonable cost)
- Second Line in Adults
- $

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Treatment: Stool Transplant

- Fecal microbiota transplantation is recommended for patients with multiple recurrences of C. difficile infection
- In whom appropriate antibiotic therapy has been ineffective

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FMT Fecal Microbiota Transplant

- 3 separate safety alerts have been published by the U.S. Food and Drug Administration (FDA) since June of 2019
  - Transmission of pathogenic Escherichia coli from donor to FMT recipients
  - Potential for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Recommended only for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments
- Screening of donor and donor fecal specimens has been performed

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Probiotics

- Recommended as a option for regular diarrhea
- Not endorsed by IDSA for C. diff because of lack of standardization of probiotics (variable colony counts, species, and possible toxicity)

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Prevention

- Optimize antibiotic prescription (stewardship)
- Use the recommended testing strategy
- Rapidly identifying and isolating patients with C. diff
- Wearing gloves and gowns when treating patients with C. diff
- Hand sanitizer doesn't kill C. diff
- Cleaning surfaces in rooms where C. diff patients are treated with EPA-approved spore killing disinfectant

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Infection Control Patient

- Notify HCP you have had infection
- Wash Hands with soap & water after using restroom and before eating
- Use separate restroom if having diarrhea
- Shower with soap

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Infection Control Hospital

- UV disinfectant
- Isolation
- Do not continue to test for clearance before transfer

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Summary

- Metronidazole no longer recommended
- Fixadomicin slightly higher first-line recommendation over oral Vancomycin
- Use of GDMP reflex test not c diff culture
- Do not test asymptomatic patients

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